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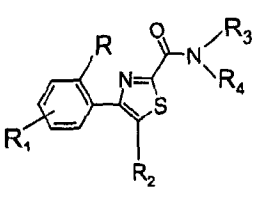
(54) Title: THIAZOLE DERIVATIVES HAVING $CB_1$-ANTAGONISTIC, AGONISTIC OR PARTIAL AGONISTIC ACTIVITY




(I)

(57) Abstract: The present invention relates to a group of thiazole derivatives which are potent antagonists, agonists or partial agonists of the cannabinoid $CB_1$-receptor. The compounds have the general formula (I) wherein R and $R_1$-$R_4$ have the meanings given in the specification.

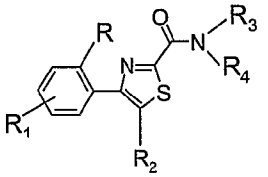
Thiazole derivatives having $CB_1$-antagonistic, agonistic or partial agonistic activity

The present invention relates to a group of thiazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned thiazole derivatives are potent cannabinoid ($CB_1$) receptor antagonists, $CB_1$ receptor agonists or $CB_1$ receptor partial agonists, with utility for the treatment of psychiatric and neurological disorders and other diseases involving cannabinoid $CB_1$ neurotransmission.

4,5-Diarylthiazole derivatives have been described in EP 388909 and EP 377457 as 5-lipoxygenase inhibitors for the treatment of thrombosis, hypertension, allergy and inflammation. The exemplified structures therein all contain two phenyl rings which are p-substituted with a methoxy, fluoro, methylthio or methylsulfinyl group. WO 9603392 describes sulfonylaryl-arylthiazoles for inflammation and pain, arthritis or fever as inflammation-associated disorders. JP 05345772 relates to 4,5-diarylthiazoles as acetyl cholinesterase inhibitors, and JP 04154773 describes 4,5-diarylthiazoles having analgesic, antiinflammatory and antipyretic action.

It has now surprisingly been found that the 4,5-diarylthiazole derivatives of the formula (I), pro-drugs thereof and salts thereof




(I)

wherein

- R represents a hydrogen atom or a substituent X from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched alkyl($C_{1-3}$)sulfonyl, carboxyl, cyano, carbamoyl, branched or unbranched dialkyl($C_{1-3}$) aminosulfonyl, branched or unbranched monoalkyl($C_{1-3}$)-aminosulfonyl and acetyl,
- $R_1$ is a hydrogen atom or represents 1-4 substituents X, wherein X has the abovementioned meaning,
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with 1-4 substituents X, wherein X has the abovementioned meaning or $R_2$ represents naphtyl,

- $R_3$ represents a hydrogen atom or a branched or unbranched $C_{1-10}$ alkyl or cycloalkyl-alkyl group or a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkylsulfonyl, dimethylsulfamido, branched or unbranched $C_{1-3}$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or $R_3$ represents a pyridyl or thienyl group,
- $R_4$ represents branched or unbranched $C_{1-10}$ alkyl or cycloalkyl-alkyl group, branched or unbranched $C_{1-10}$ alkoxy, $C_{3-8}$ cycloalkyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl, branched or unbranched $C_{3-10}$ alkenyl, $C_{5-8}$ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or $R_4$ represents a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, wherein Z has the abovementioned meaning, or $R_4$ represents a pyridyl or thienyl group, or $R_4$ represents a group $NR_5R_6$ wherein
  $R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom, or
- $R_3$ and $R_4$ – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom,

are potent antagonists, agonists or partial agonists of the cannabinoid $CB_1$ receptor.

A pro-drug is an inactive compound, which when absorbed is converted into an active form (Medicinal Chemistry: Principles and Practice, 1994, ISBN 0-85186-494-5, Ed.: F. D. King, p. 216).

Due to the potent $CB_1$ receptor activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle

spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

The affinity of the compounds of the invention for cannabinoid $CB_1$ receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid $CB_1$ receptor is stably transfected in conjunction with [$^3$H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [$^3$H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid $CB_1$ receptor antagonistic, agonistic or partial agonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid $CB_1$ receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of $CB_1$ receptors by $CB_1$ receptor agonists (*e.g.* CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This $CB_1$ receptor-mediated response can be antagonised by $CB_1$ receptor antagonists or partial agonists such as the compounds of the invention.

Cannabinoid receptor agonistic or partial agonistic activity of compounds of the invention can be determined according to published methods, such as assessment of in vivo cannabimimetic effects (Wiley, J. L. et al., J. *Pharmacol. Exp. Ther.* **2001**, *296*, 1013).
Cannabinoid receptor antagonists may behave as inverse agonists (Landsman, R. S. et al., *Eur. J. Pharmacol.* **1997**, *334*, R1-R2).

The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (I).

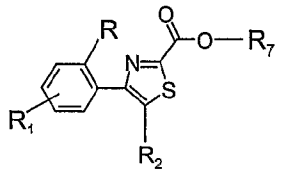
The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

A suitable synthesis for the compounds according to the present invention is the following:

Synthesis route A

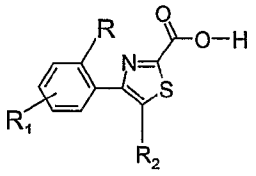
Step 1 of route A

Ester hydrolysis of a compound having formula (II) wherein $R_7$ represents a branched or unbranched alkyl group ($C_{1-4}$) or benzyl group.



(II)

This reaction gives a compound having formula (III)



(III)

wherein R, $R_1$ and $R_2$ have the meanings as described hereinabove.

The compounds of the invention having formula (II), wherein $R_7$ represents a branched or unbranched alkyl group ($C_{1-4}$) or benzyl group can be obtained according to methods known, for example:

a) Organic Reactions, Vol. VI, (1951), p. 367-409, Ed. R. Adams, John Wiley and Sons Inc., New York
b) J. S. Carter et al., *Bioorg. Med. Chem. Lett.* (1999), 9, 1167-1170
c) T. T. Sakai et al., *Bioorg. Med. Chem.* (1999), 7, 1559-1566
d) A. Tanaka et al., *J. Med. Chem.* (1994), 37, 1189-1199
e) J. J. Talley et al., WO 9603392: Chem. Abstr. 125, 33628
f) V. Cecchetti et al., *Bioorg. Med. Chem.* (1994), 2, 799-806

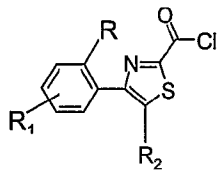
Step 2 of route A

Reaction of a compound having formula (III) with a compound having formula $R_3R_4NH$ wherein $R_3$ and $R_4$ have the meanings as described hereinabove *via* activating and coupling methods such as formation of an active ester, or in the presence of a so-called coupling reagent, such as for example, DCC, HBTU, BOP,

CIP (2-chloro-1,3-dimethylimidazolinium hexafluorophosphate), PyAOP (7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate) and the like. (For more information on activating and coupling methods see a) M. Bodanszky, A. Bodanszky: The Practice of Peptide Synthesis, Springer-Verlag, New York, 1994; ISBN: 0-387-57505-7; b) K. Akaji et al., *Tetrahedron Lett.* (1994), 35, 3315-3318; c) F. Albericio et al., *Tetrahedron Lett.* (1997), 38, 4853-4856).

This reaction gives a desired thiazole derivative having formula (I).

Alternatively, a compound having formula (III) is reacted with a so-called halogenating agent such as for example thionyl chloride ($SOCl_2$). This reaction gives the corresponding carbonyl chloride (IV).




(IV)

Reaction of a compound having formula (IV) with a compound having formula $R_3R_4NH$ wherein wherein $R_3$ and $R_4$ have the meanings as described hereinabove gives a thiazole derivative having formula (I). This reaction is preferably carried out in the presence of an organic base such as for example diisopropylethylamine (DIPEA) or triethylamine.

Alternatively, a compound having formula (II) is reacted in a so-called amidation reaction with a compound having formula $R_3R_4NH$ wherein $R_3$ and $R_4$ have the meanings as described hereinabove to give a thiazole derivative having formula (I). Such amidation reactions can be promoted by the use of trimethylaluminum $Al(CH_3)_3$ (For more information on aluminum-mediated conversion of esters to amides, see: J. I. Levin, E. Turos, S. M. Weinreb, *Synth Commun.* (1982), *12*, 989-993.)

Alternatively, a compound having formula $R_3R_4NH$ can be reacted with a strong base, such as lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LiHMDS), potassium hexamethyldisilazide (KHMDS) or sodium hexamethyldisilazide (NaHMDS) and the like to give in situ a compound having formula $R_3R_4NLi$, $R_3R_4NK$ or $R_3R_4NNa$, respectively, which can then be reacted with a compound having formula (II) to give a thiazole derivative having formula (I).

Alternatively, a compound having formula (I) wherein $R_3$ and $R_4$ represent a hydrogen atom can be reacted with a strong base, such as LDA, LiHMDS, NaH and the like, followed by a reaction with a compound L-$R_4$ wherein L represents a so-

called leaving group such as Br, Cl, I and the like, and $R_4$ represents a branched or unbranched $C_{1-10}$ alkyl group, cycloalkyl-alkyl group or a branched or unbranched $C_{3-10}$ alkenyl group, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms.

Example I

**Part A**: Magnesium (3.04 gram, 0.125 mol) is suspended in anhydrous diethyl ether (500 mL) under a nitrogen atmosphere and an iodine crystal is added. A solution of 4-chlorobenzyl chloride (20.12 gram, 0.125 mol) in anhydrous diethyl ether (100 mL) is slowly added to maintain a gentle reflux. After cooling the resulting mixture to room temperature a solution of 2,4-dichlorobenzonitrile (17.2 gram, 0.10 mol) in toluene (100 mL) is slowly added. Temperature is raised to 135 °C and the diethyl ether is removed by distillation, toluene is added and the resulting mixture is refluxed for two additional hours. After cooling to room temperature a solution of HCl (1N, 400 mL) is slowly added under cooling and stirring. The resulting mixture is extracted twice with diethyl ether, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (dichloromethane) gives 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone as a yellow oil (19.96 gram, 67 % yield). Crystallisation from cyclohexane gives pure 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone. Melting point: 65-66 °C. $^1$H-NMR (200 MHz, $CDCl_3$): δ 7.02-7.45 (m, 7H), 4.22 (s, 2H).

**Part B**: To a solution of 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (2.82 gram, 9.42 mmol) in benzene (25 mL) is added bromine (0.48 mL, 1.49 gram, 9.31 mmol) and the resulting solution is stirred at room temperature for two hours. Dichloromethane is added and the resulting solution is washed with aqueous $NaHCO_3$ solution. The organic layer is dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 3.55 gram (quantitative yield) of 2-bromo-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone as a yellow oil (purity ~ 95 % according to HPLC analysis). $^1$H-NMR (200 MHz, $CDCl_3$): δ 7.00-7.50 (m, 7H), 6.16 (s, 1H).
Analogously was prepared:
2-Bromo-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethanone. $^1$H-NMR (200 MHz, $CDCl_3$): δ 7.95 (d, J = 8 Hz, 2H), 7.23-7.62 (m, 5H), 6.77 (s, 1H).

**Part C**; 2-Bromo-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (9.83 gram, 26.0 mmol) and ethyl thiooxamate (5.28 gram, 39.6 mmol) are dissolved in absolute ethanol (50 mL). The resulting red solution is heated at reflux temperature for 4 hours. After evaporation *in vacuo* the crude red material (14 gram) is suspended in a mixture of dichloromethane and methyl-tert-butyl ether. The formed solids are removed by filtration. The resulting filtrate is purified by column chromatography (eluant: dichloromethane: $R_f$ ~0.4) to give ethyl-5-(4-chlorophenyl)-4-(2,4-

dichlorophenyl)thiazole-2-carboxylate as a yellow oil (5.21 gram, 48 % yield) which slowly solidifies. Melting point: 117-118 °C. $^1$H-NMR (200 MHz, $CDCl_3$): δ 7.53, (d, J= 2Hz, 1H), 7.40 (dt, J= 8 Hz, J = 2 Hz, 2H), 7.22-7.35 (m, 4H), 4.52 (q, J = 7 Hz, 2H), 1.45 (t, J = 7 Hz, 3H).

Analogously was prepared:
Ethyl-4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylate.

**Part D**; Ethyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.00 gram, 2.42 mmol) is added to 1-aminopiperidine (10 mL) and the resulting stirred mixture is heated at 50 °C for 4 hours. Dichloromethane is added and the resulting solution is washed twice with water, dried over $MgSO_4$, filtered and most of the dichloromethane is removed by evaporation *in vacuo*. Diisopropyl ether is added and the formed precipitate is removed by filtration. The filtrate is concentrated *in vacuo* and purified by flash chromatography (ethyl acetate: petroleum ether (40-60) = 1:3 (v/v)) to produce 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-(1-piperidinyl)thiazole-2-carboxamide (330 mg, 29 % yield) as a white foam. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.47 (t, J = 2Hz, 1H), 7.24-7.32 (m, 4H), 7.13 (dt, J = 8 Hz, J = 2Hz, 2H), 2.85-2.93 (m, 4H), 1.40-1.82 (m, 6H).

Analogously were prepared:
4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(1-piperidinyl)thiazole-2-carboxamide. Melting point: 190-191 °C. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.51 (d, J = 2 Hz, 1H), 7.22-7.38 (m, 6H), 2.90-2.97 (m, 4H), 1.75-1.84 (m, 4H), 1.44-1.52 (m, 2H).
5-(4-Chlorophenyl)-N-cycloheptyl-4-(2,4-dichlorophenyl)thiazole-2-carboxamide. Melting point: 159-161 °C.
5-(4-Chlorophenyl)-N-cyclopentyl-4-(2,4-dichlorophenyl)thiazole-2-carboxamide. Melting point: 111-113 °C.
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(trans-4-hydroxycyclohexyl)thiazole-2-carboxamide. Melting point: 109 °C.
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(2-methylcyclohexyl)thiazole-2-carboxamide. Melting point: 134-147 °C.
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(4-fluorobenzyl)thiazole-2-carboxamide. Melting point: 142-144 °C.
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(trans-4-methylcyclohexyl)thiazole-2-carboxamide. Melting point: 165-166 °C.
5-(4-Chlorophenyl)-N-(cis-4-methylcyclohexyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide. Melting point: 72 °C.

## Example 2

**Part A**; Ethyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (4.10 gram, 9.93 mmol) is suspended in methanol (75 mL). A solution of KOH (1.98 gram, 30 mmol) in water (75 mL) is added and the resulting mixture is heated at reflux

temperature for 2 hours. The resulting yellow solution is allowed to attain room temperature, poured into water and acidified with 1N aqueous HCl to give a white precipitate. This precipitate is collected by filtration and twice washed with water. Drying *in vacuo* gives 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid as a white solid (2.59 gram, 68 % yield). $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 9.25 (s, 1H), 7.65-7.72 (m, 1H), 7.28-7.52 (m, 6H).

Analogously was prepared:

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid

**Part B**; 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid (1.00 gram, 2.6 mmol) is suspended in anhydrous acetonitrile (20 mL) under a nitrogen atmosphere at room temperature. Diisopropylethylamine (DIPEA) ( 1.36 mL, 7.8 mmol), O-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluorophosphate (HBTU) (1.08 gram, 2.85 mmol) and O-*tert*-butylhydroxylamine.HCl (0.35 gram, 25.1 mmol) are successively added and the resulting mixture is stirred overnight at room temperature. The resulting mixture is concentrated *in vacuo* and dichloromethane is added. The resulting solution is successively washed with water and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. Subsequent flash chromatography (ethyl acetate:petroleum ether (40-60) = 1:3 (v/v)) gives N-(t-butoxy)-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide (0.60 gram, 51 % yield) as a white foam. $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.47 (t, J = 2 Hz, 1H), 7.25-7.31 (m, 4H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 1.36 (s, 9H).

Analogously were prepared:

N-(t-Butoxy)-4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxamide. $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.52 (d, J = 2 Hz, 1H), 7.35 (dt, J = 8 Hz, J = 2 Hz, 2H) 7.23-7.31 (m, 4H), 1.40 (s, 9H).

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(*n*-pentyl)thiazole-2-carboxamide

$^1$H-NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.21-7.32 (m, 5H), 7.14 (dt, J = 8 Hz, J = 2Hz, 2H), 3.42-3.48 (m, 2H), 1.59-1.67 (m, 2H), 1.30-1.40 (m, 4H), 0.90 (t, J = 7 Hz, 3H).

5-(4-Chlorophenyl)-N-cyclohexyl-4-(2,4-dichlorophenyl)thiazole-2-carboxamide

$^1$H-NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.24-7.35 (m, 4H), 7.05-7.17 (m, 3H), 3.90-4.00 (m, 1H), 1.98-2.07 (m, 2H), 1.72-1.82 (m, 2H), 1.14-1.70 (m, 6H).

## Example 3

**Part A**; To 4-bromobenzaldehyde (25 gram, 0.135 mol) is successively added 2,4-dichlorophenylacetic acid (27.7 gram, 0.135 mol), acetic anhydride (100 mL) and triethylamine (19 mL, 0.136 mol) and the resulting mixture is heated at reflux temperature for 90 minutes. The reaction mixture is cooled to 110 °C and water (100 mL) is slowly added. The resulting mixture is allowed to attain room temperature and ethyl acetate is added. The ethyl acetate layer is twice washed with water, dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil is crystallised from diisopropyl ether to give 3-(4-bromophenyl)-2-(2,4-dichlorophenyl)acrylic acid as a white solid (26.55 gram, 53 % yield).

**Part B**; 3-(4-Bromophenyl)-2-(2,4-dichlorophenyl)acrylic acid (26.55 gram, 71 mmol) is dissolved in anhydrous toluene (130 mL) and the resulting solution is cooled to 0 °C. Triethylamine (7.40 gram, 73 mmol) and diphenylphosphoryl azide (19.8 gram, 72 mmol) are successively added and the resulting mixture is stirred at 0 °C for 20 minutes and 150 minutes at room temperature. The reaction mixture is poured into water and extracted three times with diethyl ether. The collected organic layers are dried over $MgSO_4$ and the diethyl ether is removed *in vacuo*. The resulting toluene layer is slowly added to refluxing toluene (150 mL). t-Butanol is added after 90 minutes and heating at reflux temperature is continued for 1 hour, followed by slow addition of concentrated hydrochloric acid (5 mL). After stirring the resulting solution overnight at 90 °C it is allowed to attain room temperature, washed twice with water, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a yellow oil. This oil is crystallised from n-hexane to give 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)ethanone (14.72 gram, 60 % yield). Melting point: 69-70 °C.

**Part C**: To a solution of 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)ethanone (5.00 gram, 15 mmol) in benzene (50 mL) is dropwise added bromine (0.75 mL, 15 mmol) and the resulting solution is stirred for 4 hours at room temperature and concentrated *in vacuo*. Dichloromethane is added and the resulting solution is washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 2-bromo-2-(4-bromophenyl)-1-(2,4-dichlorophenyl)ethanone as an oil (5.96 gram, 94 % yield).

**Part D**: A solution containing 2-bromo-2-(4-bromophenyl)-1-(2,4-dichlorophenyl)ethanone (5.96 gram, 14 mmol) and ethyl thiooxamate (2.80 gram, 21 mmol) in ethanol (30 mL) is heated at reflux temperature for four hours. After cooling to room temperature the precipitated crystalline material is removed by filtration. The filtrate is concentrated *in vacuo* and the resulting material (7.56 gram orange oil) is purified by flash chromatography (ethyl acetate/petroleum ether = 1/3 (v/v)) and subsequently crystallised from diisopropyl ether to afford ethyl 5-(4-bromophenyl)-4-(2,4-dichlorophenyl) thiazole-2-carboxylate (2.11 gram, 33 % yield). Melting point: 129-130 °C.

**Part E**: A stirred mixture containing ethyl 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.00 gram, 2.2 mmol) and 1-aminopiperidine (10 mL) is heated overnight at 50 °C. The resulting mixture is allowed to attain room temperature, dichloromethane is added and the resulting solution is twice washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Flash chromatographic purification of this oil (ethyl acetate/petroleum ether = 1/3 (v/v))

gives 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)-N-(1-piperidinyl)thiazole-2-carboxamide (870 mg, 78 % yield). Melting point: 171-173 °C.
Analogously were prepared:
4-(2,4-Dichlorophenyl)-N-(1-piperidinyl)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 181-183 °C.
N-Cyclohexyl-4-(2,4-dichlorophenyl)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 140-142 °C.
4-(2,4-Dichlorophenyl)-N-(exo-bicyclo[2.2.1]hept-2-yl)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 184-185 °C.
4-(2,4-Dichlorophenyl)-N-(4-morpholinyl)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 95 °C.

Example 4

**Part A**: Ethyl 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.80 gram, 3.94 mmol) is dissolved in methanol (20 mL) and a solution of KOH (0.65 gram (85 %), 9.85 mmol) in water (20 mL) is added. The resulting mixture is heated at reflux temperature for 1 hour, poured into water and acidified with hydrochloric acid (1N solution). The formed precipitated material is collected by filtration and dried *in vacuo* at room temperature to give a quantitative yield of 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)-thiazole-2-carboxylic acid. Melting point: 94-95 °C.

**Part B**: 5-(4-Bromophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid (0.50 gram, 1.17 mmol) and diisopropylethylamine (DIPEA) (1.02 mL, 5.85 mmol) are dissolved in dichloromethane (5 mL) and cooled to 0 °C. 7-Aza-1-hydroxybenzotriazole (HOAt) (0.11 gram, 0.81 mmol) and 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate (CIP) (0.50 gram, 1.76 mmol) are added, followed by addition of n-pentylamine (0.15 gram, 1.76 mmol) and the resulting mixture is stirred at room temperature overnight. Flash chromatographic purification (dichloromethane) gives 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)-N-(n-pentyl)thiazole-2-carboxamide as an amorphous solid (0.28 gram, 48 % yield).
Analogously were prepared:
5-(4-Bromophenyl)-4-(2,4-dichlorophenyl)-N-(hexahydro(1H)azepin-1-yl)thiazole-2-carboxamide. Melting point: 206-207 °C.
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(morpholin-4-yl)thiazole-2-carboxamide. Amorphous solid.
5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(pyrrolidin-1-yl)thiazole-2-carboxamide. Melting point: 179-181 °C.

Example 5

**Part A**: To a solution of 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid (0.50 gram, 1.30 mmol) in dichloromethane (10 mL) is successively added 1-aminohexahydro(1H)azepine (0.15 gram, 1.30 mmol), 7-aza-1-hydroxybenzotriazole (0.18 gram, 1.30 mmol), 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) (0.68 gram, 1.30 mmol) and diisopropylethylamine (0.34 mL, 1.95 mmol) and the resulting solution is stirred for 1 hour at room temperature. Concentration *in vacuo* gives a crude oil (2.01 gram) which is purified by flash chromatography (ethyl acetate/petroleum ether = 1/3 (v/v)) to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-(hexahydro(1H)azepin-1-yl)thiazole-2-carboxamide (0.350 gram, 56 % yield). Melting point: 185-186 °C (after recrystallisation from diisopropyl ether).

Analogously were prepared:

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(hexahydrocyclopenta-[c]pyrrol-2(1H)-yl)thiazole-2-carboxamide. Melting point: 173-174 °C.

N-Benzyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-methyl-thiazole-2-carboxamide. Melting point: 141-144 °C.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(4-(trifluoromethyl)benzyl) thiazole-2-carboxamide. Melting point: 174-176 °C.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(exo-bicyclo[2.2.1]hept-2-yl)thiazole-2-carboxamide. Melting point: 194-195 °C.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(endo-bicyclo[2.2.1]hept-2-yl)thiazole -2-carboxamide. Melting point: 181-183 °C.

4-(2,5-Dichlorophenyl)-N-(exo-bicyclo[2.2.1]hept-2-yl)-5-(phenyl)thiazole-2-carboxamide. Melting point: 170 °C.

N-(Cyclohexyl)-4-(2,5-dichlorophenyl)-5-(phenyl)thiazole-2-carboxamide. Melting point: 75 °C.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(tetrahydro-2H-pyran-2-yloxy)thiazole -2-carboxamide. Melting point: 85 °C.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(5,5,5-trifluoropentyl)thiazole-2-carboxamide. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.47 (br s, 1H), 7.24-7.31 (m, 5H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 3.49 (q, J = 7 Hz, 2H), 2.07-2.20 (m, 2H), 1.62-1.77 (m, 4H).

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(2-fluoroethyl)thiazole-2-carboxamide. Amorphous solid. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.52-7.58 (m, 1H), 7.47 (br s, 1H), 7.24-7.32 (m, 4H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 4.61 (dt, J = 47 Hz, J = 5 Hz, 2H), 3.72-3.84 (m, 2H).

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(5-fluoropentyl)thiazole-2-carboxamide. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.47 (br s, 1H), 7.24-7.30 (m, 5H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 4.45 (dt, J = 47 Hz, J = 6 Hz, 2H), 3.45-3.51 (m, 2H), 1.64-1.82 (m, 4H), 1.48-1.56 (m, 2H).

4-(2,5-Dichlorophenyl)-N-(4-morpholinyl)-5-(phenyl)thiazole-2-carboxamide. Melting point: 155-157 °C.

Example 6

Ethyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.65 gram, 4.0 mmol) is dissolved in anhydrous THF (25 mL) and aniline (0.37 mL, 4.0 mmol) is added. The resulting solution is cooled to 0 °C and sodium hexamethyldisilazide (4.4 mL of a 1M solution in THF) is added. The reaction mixture is stirred for 2 hours. Water is added and the mixture is extracted twice with ethyl acetate. The combined organic layer is washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is crystallised from diisopropyl ether to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-phenyl-thiazole-2-carboxamide (1.42 g, 77 % yield). Melting point: 167-168 °C.

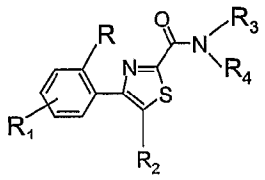
Example 7

**Part A**: Gaseous $NH_3$ is led through a stirred solution of ethyl 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.65 gram, 4.0 mmol) in methanol (25 mL) at room temperature. A small piece of sodium metal is added. After stirring the resulting mixture for three hours the precipitate is collected by filtration, washed with a small portion of methanol and dried to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide (1.16 gram, 76 % yield), melting point 195-198 °C. $^1$H-NMR (200 MHz, $CDCl_3$): δ 7.48 (br s, 1H), 7.22-7.35 (m, 4H), 7.05-7.20 (m, 3H) 5.55-5.65 (M, 1H).

**Part B**: To a cooled (0 °C) stirred solution of 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide (1.16 gram, 3.02 mmol) in anhydrous DMF (20 mL) is added NaH (0.13 gram of a 60 % dispersion) in a nitrogen atmosphere. The resulting mixture is stirred for 1 hour and excess 4,4,4-trifluoro-1-bromobutane (0.7 mL) is added. The resulting solution is stirred at room temperature for 1 hour, poured onto ice/water and extracted twice with diethyl ether. The collected diethyl ether layers are twice washed with water, dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue is further purified by column chromatography (silica gel: eluant: dichloromethane) to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-(4,4,4-trifluorobutyl)thiazole-2-carboxamide. Melting point: 99-101 °C.

## Claims

1. A compound of formula (I)



(I)

wherein

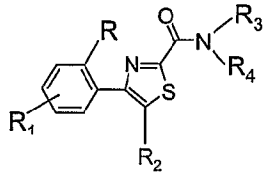
- R represents a hydrogen atom or a substituent X from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched alkyl($C_{1-3}$)sulfonyl, carboxyl, cyano, carbamoyl, branched or unbranched dialkyl($C_{1-3}$) aminosulfonyl, branched or unbranched monoalkyl($C_{1-3}$)-aminosulfonyl and acetyl,
- $R_1$ is a hydrogen atom or represents 1-4 substituents X, wherein X has the abovementioned meaning,
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with 1-4 substituents X, wherein X has the abovementioned meaning or $R_2$ represents naphtyl,
- $R_3$ represents a hydrogen atom or a branched or unbranched $C_{1-10}$ alkyl or cycloalkyl-alkyl group or a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkylsulfonyl, dimethylsulfamido, branched or unbranched $C_{1-3}$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or $R_3$ represents a pyridyl or thienyl group,
- $R_4$ represents branched or unbranched $C_{1-10}$ alkyl or cycloalkyl-alkyl group, branched or unbranched $C_{1-10}$ alkoxy, $C_{3-8}$ cycloalkyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl, branched or unbranched $C_{3-10}$ alkenyl, $C_{5-8}$ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or $R_4$ represents a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, wherein Z has the abovementioned meaning, or $R_4$ represents a pyridyl or thienyl group, or $R_4$ represents a group $NR_5R_6$ wherein

$R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom, or

- $R_3$ and $R_4$ – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom,

and pro-drugs, stereoisomers and salts thereof.

2. A compound of formula (I)



(I)

wherein

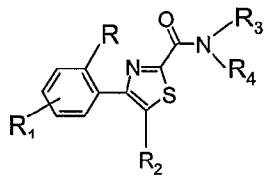
- R represents a substituent Y from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkoxycarbonyl, carboxyl, cyano, carbamoyl and acetyl,
- $R_1$ represents hydrogen or one or more substituents Y, wherein Y has the above mentioned meaning.
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or $R_2$ represents naphtyl,
- $R_3$ is hydrogen,
- $R_4$ represents branched or unbranched $C_{1-10}$ alkyl or alkyl-cycloalkyl, branched or unbranched $C_{1-10}$ alkoxy, $C_{3-8}$ cycloalkyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl, branched or unbranched $C_{3-10}$ alkenyl, $C_{5-8}$ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may optionally be substituted with a hydroxy group, 1-3 methyl groups or an ethyl group or 1-3 fluoro atoms, or $R_4$ represents a benzyl or phenethyl group which

aromatic rings may be substituted with one or more substituents Z, which can be the same or different, from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkylsulfonyl, dimethylsulfamido, branched or unbranched $C_{1-3}$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or $R_4$ represents a pyridyl or thienyl group, or $R_4$ represents a group $NR_5R_6$ wherein

$R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

3. A compound of formula (I)



(I)

wherein

- R represents a substituent Y from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkoxycarbonyl, carboxyl, cyano, carbamoyl and acetyl,
- $R_1$ represents one or more substituents Y, wherein Y has the above mentioned meaning.
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or $R_2$ represents naphtyl,
- $R_3$ is hydrogen,
- $R_4$ represents branched or unbranched $C_{1-10}$ alkyl or alkyl-cycloalkyl, branched or unbranched $C_{1-10}$ alkoxy, $C_{3-8}$ cycloalkyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl, branched or unbranched $C_{3-10}$ alkenyl, $C_{5-8}$ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may

optionally be substituted with a hydroxy group, 1-3 methyl groups or an or ethyl group or 1-3 fluoro atoms, or $R_4$ represents a benzyl or phenethyl group which aromatic rings may be substituted with one or more substituents Z, which can be the same or different, from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkylsulfonyl, dimethylsulfamido, branched or unbranched $C_{1-3}$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or $R_4$ represents a pyridyl or thienyl group, or $R_4$ represents a group $NR_5R_6$ wherein,

$R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

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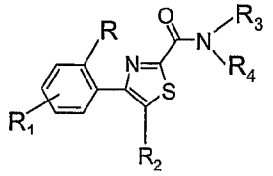

(I)

wherein

- R represents a halogen atom
- $R_1$ represents one or more substituents Y, wherein Y has the meaning as given in claim 2,
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or $R_2$ represents naphtyl,
- $R_3$ is hydrogen,
- $R_4$ represents branched or unbranched $C_{1-10}$ alkyl or alkyl-cycloalkyl, branched or unbranched $C_{1-10}$ alkoxy, $C_{3-8}$ cycloalkyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl, branched or unbranched $C_{3-10}$ alkenyl, $C_{5-8}$ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may optionally be substituted with a hydroxy group, 1-3 methyl groups or an ethyl

group or 1-3 fluoro atoms, or $R_4$ represents a benzyl or phenethyl group which aromatic rings may be substituted with one or more substituents Z, which can be the same or different, from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkylsulfonyl, dimethylsulfamido, branched or unbranched $C_{1-3}$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or $R_4$ represents a pyridyl or thienyl group, or $R_4$ represents a group $NR_5R_6$ wherein,

$R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

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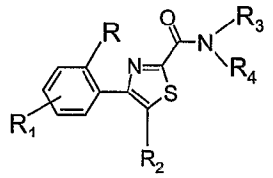


(I)

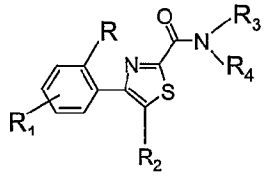
wherein

- R represents a halogen atom
- $R_1$ represents one or more substituents Y, wherein Y has the meaning as given in claim 2,
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or $R_2$ represents naphtyl,
- $R_3$ is hydrogen,
- $R_4$ represents a group $NR_5R_6$ wherein,

  $R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

6. A compound of formula (I)

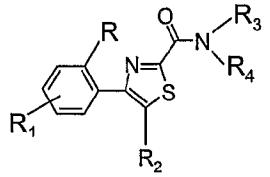


(I)

wherein

- R represents a halogen atom,
- $R_1$ represents one or more halogen atoms,
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the meaning as given in claim 2, or $R_2$ represents naphtyl,
- $R_3$ is hydrogen,
- $R_4$ represents a group $NR_5R_6$ wherein,
  $R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom,
  and pro-drugs, stereoisomers and salts thereof.

7. Use of a compound of formula (I)



(I)

wherein

- R represents a hydrogen atom or a substituent X from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched alkyl($C_{1-3}$)sulfonyl,

carboxyl, cyano, carbamoyl, branched or unbranched dialkyl($C_{1-3}$) aminosulfonyl, branched or unbranched monoalkyl($C_{1-3}$)-aminosulfonyl and acetyl,

- $R_1$ is a hydrogen atom or represents 1-4 substituents X, wherein X has the abovementioned meaning,
- $R_2$ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with 1-4 substituents X, wherein X has the abovementioned meaning or $R_2$ represents naphtyl,
- $R_3$ represents a hydrogen atom or a branched or unbranched $C_{1-10}$ alkyl or cycloalkyl-alkyl group or a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group branched or unbranched $C_{1-3}$-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, branched or unbranched ($C_{1-3}$)-alkylsulfonyl, dimethylsulfamido, branched or unbranched $C_{1-3}$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or $R_3$ represents a pyridyl or thienyl group,
- $R_4$ represents branched or unbranched $C_{1-10}$ alkyl or cycloalkyl-alkyl group, branched or unbranched $C_{1-10}$ alkoxy, $C_{3-8}$ cycloalkyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl, branched or unbranched $C_{3-10}$ alkenyl, $C_{5-8}$ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or $R_4$ represents a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, wherein Z has the abovementioned meaning, or $R_4$ represents a pyridyl or thienyl group, or $R_4$ represents a group $NR_5R_6$ wherein

  $R_5$ and $R_6$ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom, or

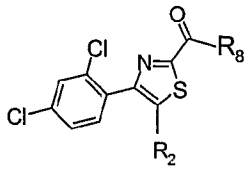
- $R_3$ and $R_4$ – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched $C_{1-3}$ alkyl, hydroxy or trifluoromethyl group or a fluoro atom, and pro-drugs, stereoisomers and salts thereof,

for the preparation of a pharmaceutical composition for the treatment of disorders involving $CB_1$ cannabinoid neurotransmission such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle

spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, plaque sclerosis, viral encephalitis, demyelinisation related disorders and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders

8. A pharmaceutical composition containing at least one compound as claimed in one of the claims 1-7 as an active component.

9. A compound of formula (V)




(V)

wherein $R_2$ has the meaning as given in claim 1 and $R_8$ represents a hydroxy group, a branched or unbranched alkoxy ($C_{1-4}$) group, a benzyloxy group or a chloro atom.

10. Use of a compound as claimed in one of the claims 1-7 for the preparation of a pharmaceutical composition for the treatment of disorders involving $CB_1$ cannabinoid neurotransmission such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, plaque sclerosis, viral encephalitis, demyelinisation related disorders and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50063

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/68 A61K31/425 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 June 2003 | 25/06/2003 |

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|---|---|
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